

## Review Article

# Early Detection and Treatment of Psychosis: The Bern Child and Adolescent Psychiatric Perspective

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Commonly conceptualized as neurodevelopmental disorders of yet poorly understood aetiology, schizophrenia and other nonorganic psychoses remain one of the most debilitating illnesses with often poor outcome despite all progress in treatment of the manifest disorder. Drawing on the frequent poor outcome of psychosis and its association with the frequently extended periods of untreated first-episode psychosis (FEP) including its prodrome, an early detection and treatment of both the FEP and the preceding at-risk mental state (ARMS) have been increasingly studied. Thereby both approaches are confronted with different problems, for example, treatment engagement in FEP and predictive accuracy in ARMS. They share, however, the problems related to the lack of understanding of developmental, that is, age-related, peculiarities and of the presentation and natural course of their cardinal symptoms in the community. Most research on early detection and intervention in FEP and ARMS is still related to clinical psychiatric samples, and little is known about symptom presentation and burden and help-seeking in the general population related to these experiences. Furthermore, in particular in the early detection of an ARMS, studies often address adolescents and young adults alike without consideration of developmental characteristics, thereby applying risk criteria that have been developed predominately in adults. Combining our earlier experiences described in this paper in child and adolescent, and general psychiatry as well as in both lines of research, that is, on early psychosis and its treatment and on the early detection of psychosis, in particular in its very early states by subjective disturbances in terms of basic symptoms, age-related developmental and epidemiological aspects have therefore been made the focus of our current studies in Bern, thus making our line of research unique.

## 1. Introduction

Schizophrenia and other nonorganic psychoses remain one of the most debilitating illnesses [1, 2], despite all the progress in treatment that has been made since the introduction of antipsychotics in the 1960s. Though generally conceptualized as a neurodevelopmental disorder, their aetiology is still only poorly understood. Psychotic disorders have a life-time prevalence of approximately 3.5% [3] and a 12-month incidence rate of about 0.035% [4]. They usually first strike early in life, between the ages of 20 and 25 [4, 5]; approximately 10–15% are early-onset psychoses (EOP) manifesting themselves before the age of 18, and approximately 1–3% are very-early-onset psychoses (VEOP) with an onset before the age of 13 [6]. Despite their relatively low prevalence, psychoses are

one of the top-ten diseases with regard to disability-adjusted life years (DALYs) [7–9]. Furthermore, the immense indirect costs of these disorders, for example, caused by early and lasting loss of productivity on the part of both patients and their carers, make them one of the most costly disorders for society [8, 9].

The high societal and personal cost are driven in part by the poor course that psychoses tend to take after their initial manifestation. A poor course however is, among others, a consequence of the frequently long duration of unrecognized and untreated psychosis (DUP) and illness, including the prodrome (DUI) [10–13] even in persons seeking help early [14, 15]. An extended prodrome of more than three years precedes the majority of first-episode psychoses (FEP) [13, 16, 17]; however, the gradual progression characteristic of

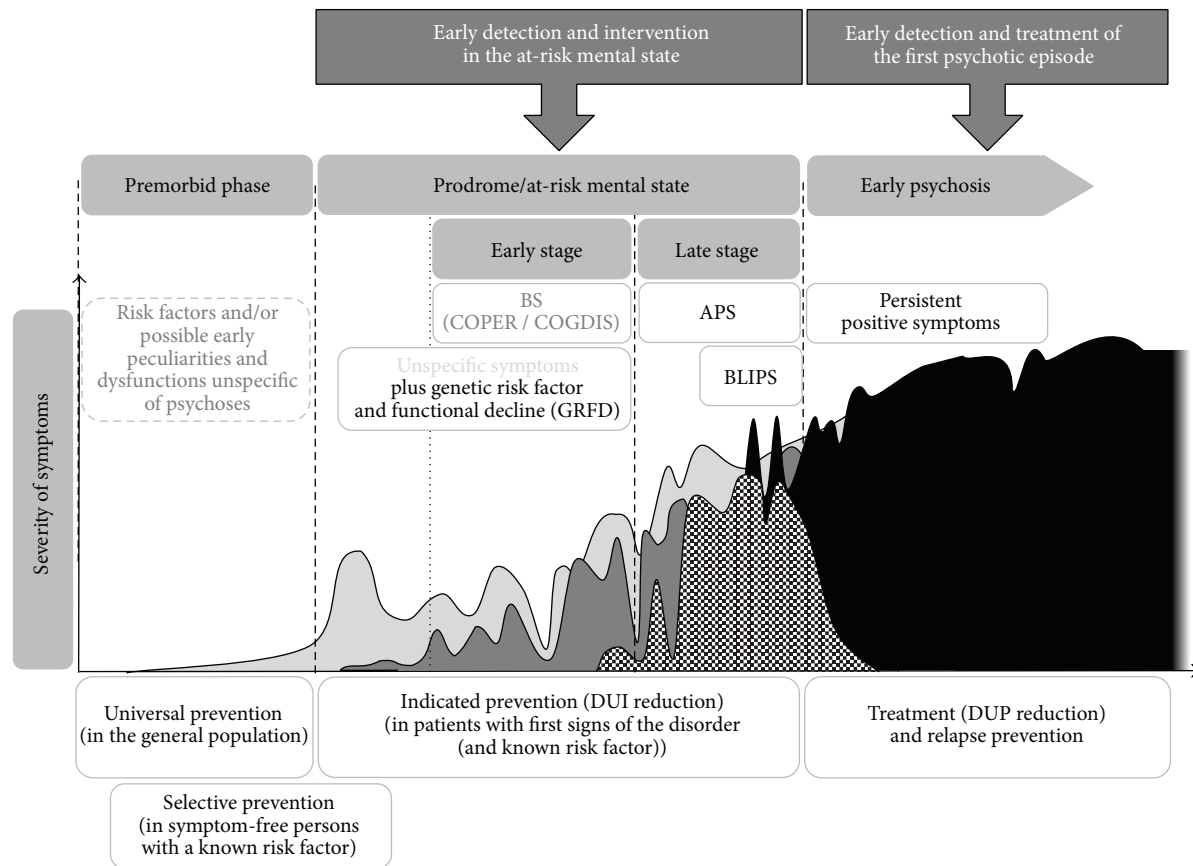


FIGURE 1: Hypothetical early course of psychosis in relation to primary and secondary preventive approaches (according to [164]). Annotations: BS: basic symptoms; COPER: cognitive-perceptive basic symptoms; COGDIS: cognitive disturbances; APS: attenuated psychotic symptoms; BLIPS: brief limited intermittent psychotic symptoms; DUP: duration of untreated psychosis; DUI: duration of untreated illness.

psychoses impedes the identification of a disorder by patients and healthcare professionals. Thus, since the 1990s, efforts have increasingly focused on detecting and treating FEP early, preferably, in terms of indicated prevention, while the patient is still within the prodromal state and before the onset of persisting positive psychotic symptoms (Figure 1) [18–20].

As an example of these efforts, the present outlook paper will summarize the research conducted by the two authors, both being experts in this area of research, and their perspectives on it and conclude with an outlook on future questions that will have to be addressed.

## 2. The First Episode of Psychoses

**2.1. The Melbourne Early Psychosis Prevention and Intervention Centre (EPPIC).** The Early Psychosis Prevention and Intervention Centre (EPPIC) in Melbourne has been one of the first programmes with a mandate to detect and treat all patients with FEP of both early and young adult onset (mid-teens to midtwenties) [21]. Gradually developing between 1984 and 1992, EPPIC services a sector with a population of about 800,000 people. Working within a national mental health system, it receives all referrals with suspicion of a FEP. Thus, its database provides a unique and, in terms of sampling, unbiased opportunity to analyse the characteristics

and treatment outcomes of all types of FEP [22–30] and has a special focus on bipolar psychoses [23, 31, 32]. Such detailed knowledge is important for identifying obstacles to care and for detecting starting-points for early detection and intervention in FEP and has therefore been in the special focus of the work of Benno Schimmelmann.

**2.1.1. The Early Course of First-Episode Psychosis.** One important finding of the EPPIC data was that diagnostic stability over 18 months is high for first episodes of schizophrenic psychoses with few shifts from schizophrenia to other diagnoses. On the other hand, patients with a FEP diagnosis of schizophreniform or bipolar disorder were diagnostically unstable, with frequent shifts to other psychotic disorders, mainly schizophrenia, necessitating longitudinal reassessment of their diagnoses [33]. Thus, after their first episode, most psychoses had a poor outcome within the first 18 months with the frequency of the diagnosis of its most severe type, schizophrenia, increasing. Thereby, persistent substance use over the treatment period but not baseline substance use was associated with nonremission of psychotic symptoms after 18 months, even after controlling for many relevant predictors of outcome [34]. Similarly, persistent cannabis use but not cannabis use at baseline was a significant predictor of worse outcome in early-onset psychosis [35]. Additionally cannabis

use disorders starting before age 14 seem to predict an earlier onset of psychosis [36]; an earlier onset, in turn, had been associated with a poorer outcome [16]. Thus, substance and in particular cannabis use seem to have differential and age-related effects on the course of psychosis: accelerating the onset of psychosis in young psychosis-prone adolescents and corrupting the outcome of FEP in general, that is, across all age groups.

**2.1.2. Treatment Compliance in First-Episode Psychosis.** Adherence to treatment and medication is a significant problem in early psychosis. In the FEP cohort of EPPIC ( $N = 661$ ), 19% never took the prescribed medication and 23% disengaged from the program despite significant efforts to keep patients engaged in treatment (such as assertive community treatment, specific crisis teams, and highly specialized case managers). Predictors of service disengagement and medication nonadherence or refusal were persistent substance use over the treatment period, a forensic history, and lack of family support [37, 38]. Those consistently refusing all medications from the outset were more likely to have a forensic history compared to those who became nonadherent later on [38]. Service disengagement was further predicted by moderate illness severity and a lack of significant treatment success until disengagement from both the entire sample and the adolescent subsample [37, 39].

**2.1.3. Early-Onset and Adult Onset Psychosis.** With regard to developmental peculiarities, the EPPIC cohort has provided a unique opportunity to assess differences between EOP and young adult onset psychosis (AOP; starting between ages 18 and 28). Due to EPPIC's focus on a young age range, about 19% of the sample was EOP patients (onset between 8.2 and 17.9 years). Compared to AOP patients, EOP had a slightly lower premorbid functioning and considerably longer duration of untreated psychosis (median 26.3 weeks in EOP compared to 8.7 weeks in AOP). Notably, the significantly longer DUP in EOP accounted for their worse course after controlling for type of psychosis, level of premorbid functioning, family support, and psychiatric history. No significant outcome differences including illness severity, global functioning, remission of positive symptoms, or employment status were detected between EOP and AOP [40, 41]. Hence the negative effects of DUI and DUP may be exacerbated in EOP. The treatment delay observed in EOP may be due to several factors, including the more pronounced neurodevelopmental and cognitive deficits, the insidious onset of less pronounced positive symptoms, and/or the atypical clinical picture of the beginning EOP—potentially misinterpreted as “adolescent crisis” [40]. Furthermore, as the age of onset of symptoms seems to be earlier in adolescent cannabis users [42], early symptoms might also be mistaken as substance-induced. Thus, early detection and treatment of persons with the first signs of the disorder, which is currently regarded as a promising strategy in fighting the consequences of psychosis, may face different or additional challenges in EOP as compared to AOP.

**2.2. The Hamburg Psychosis Early Detection and Intervention Project (PEDIC).** Based on the EPPIC experience, the Psychosis Early Detection and Intervention Project (PEDIC) was implemented in Hamburg in 2003. One early research focus of PEDIC was on remission and recovery of symptoms, functioning, and subjective well-being in adults with FEP [43–45].

**2.2.1. Remission and Recovery in First-Episode Schizophrenia.** In a 3-year follow-up study of 392 never-treated patients with schizophrenia cared for within PEDIC, remission rates were 60% for symptoms, 45% for functional deficits, and 57% for subjective well-being; corresponding recovery rates were 52%, 35%, and 44%; 28% were in combined remission and 17% in combined recovery (fulfilling all remission or recovery criteria, resp.). Studies examining predictors of remission and functional outcome have shown that premorbid and baseline psychosocial functioning and good treatment response with symptom remission within the first 3 months are the best predictors of both [45–51]. These findings have important clinical implications whereby the low proportion of patients who met remission or recovery criteria clearly highlights the importance of making adaptations to treatment early on [45]. Furthermore, our studies suggested that measures of quality of life and subjective well-being should be assessed when measuring the outcome of psychotic disorders [52–54]. The patient's perspective and experience might be particularly important when it comes to assessment of the side effects of antipsychotics. Because objective and subjective side effects often differ and subjective impairment may be a stronger predictor of nonadherence than objective measures of the severity of side effects, assessing both objective and subjective side effects has been strongly recommended [54].

**2.2.2. Assertive Community Treatment in Schizophrenia-Spectrum Disorders: The Access Trial.** Despite all of the knowledge gained about moderators of outcome in FEP, a crucial, yet unresolved, question is how patients with psychotic disorders are optimally treated. In Hamburg, we constructed a comprehensive treatment model for patients with both first- and multiple-episode schizophrenia-spectrum disorders, the ACCESS model, which included assertive community treatment, specialized personnel, integration of specific treatment options for psychotic patients such as cognitive-behavioural psychotherapy, metacognitive training, and a general psychotherapeutic approach including techniques of open dialogue [55–57]. At 12 months, patients treated in the ACCESS program had better outcomes than those treated as usual in an integrated care setting without assertive community treatment, case management, or specialized personnel in terms of service engagement, symptoms, functioning, quality of life, and satisfaction with care. The additional treatment effect of the ACCESS program was clearly significant, and the costs of ACCESS were similar to treatment as usual; therefore inpatient days were significantly decreased while outpatient contacts were increased [58, 59]. ACCESS was then translated into clinical practice and extended to bipolar psychotic disorders. The benefits of

the ACCESS treatment model, particularly in terms of high service engagement and low hospitalization rates, remained stable over a 2-year period [60], yet their longer-term effects remain to be studied.

*2.3. Getting There Even Earlier: Lessons from First-Episode Psychosis Research.* Despite a broad range of efforts to improve the outcome of FEP but also of multipisode psychosis, many patients continue to suffer from symptoms as well as poor functioning and quality of life. Thus, not only is the early identification of patients with manifest psychotic disorders important in order to reduce the DUP [41], but also the early detection of at-risk mental states (ARMS) is mandatory for the reduction of DUI and the burden of psychotic disorders in both adults [61] and children and adolescents [62–65].

### 3. The At-Risk Mental State

Since Kraepelin's description of dementia praecox more than a century ago [66], diagnosis, treatment, and studies of psychosis have focused mainly on its cardinal positive and negative symptoms. In the last two decades, however, the growing interest in prodromal or risk states of the illness has generated renewed interest in the early subclinical expressions and subtle, self-experienced changes in mentation that had already been observed by Kraepelin [66, 67].

Until the 1980s, scattered and mainly retrospective reports of the psychotic prodrome prevailed that led to the formulation of early developmental models of schizophrenia such as Conrad's [68] and Docherty's [69] staging models, both assuming a unidirectional mandatory pattern of symptom manifestation. These invariant models, however, could not be confirmed by retrospective data on the early course assessed on FEP patients in the Age, Beginning, Course (ABC) study [16, 70], suggesting that the road to psychosis might not be a straight one but rather twisted with stops and returns being possible at any stage [71, 72]. Thus, not knowing where the road is leading when looking at it prospectively, there is common agreement in prospective research nowadays not to use the retrospectively defined term "prodrome" that would indicate that a certain outcome is inevitable but to emphasise the risk along with the only more or less probable outcome. To this end, several terms have been proposed that are often used and considered interchangeable, even if they originally related to distinct concepts or assessments. This fact has unfortunately created Babylonian speech confusion as well as heterogeneity and variance of findings [73, 74]. In the following, the term "at-risk mental state" (ARMS) that is not linked to a specific operationalization or assessment is used when prospectively relating to a state which may be the prodrome of a FEP.

*3.1. Symptomatic Risk Criteria for First-Episode Psychosis.* For the indicated prevention of psychosis in help-seeking persons already suffering from first signs and symptoms of the emerging disorder, two approaches were developed in parallel [75]. Both approaches distinguish between affective and nonaffective psychotic disorders and nonpsychotic affective disorders [76, 77]: the basic symptom (BS) approach

targeting the earliest possible specific risk symptoms by our Cologne group and the ultrahigh risk (UHR) approach targeting an imminent risk of psychosis with a conversion within the next 12 months by the Melbourne and New Haven groups of Patrick McGorry and Thomas McGlashan (Figure 1).

#### 3.1.1. Basic Symptom Criteria

*(1) The Basic Symptom Concept.* Relating to early descriptions of prodromal changes by Mayer-Gross [78], the most thorough early description of subtle early symptoms has been provided within the framework of the BS concept [20, 71, 79]. BS are subtle, subjectively experienced subclinical disturbances in drive, stress tolerance, affect, thinking, speech, attention, body and sensory perception, and motor action [71]. These subjective symptoms were regarded as the earliest perceivable signs of the developing psychotic disorder and its neurobiological correlates—hence the term "basic" [20]. Although BS vary in their specificity for psychoses and can occur in nonpsychotic disorders to various degrees [76, 80, 81], they are recognized nowadays mainly for their occurrence in initial prodromal states of psychoses including potential outpost syndromes (i.e., spontaneously remitting "prodrome-like" phases preceding the prodrome leading to frank psychosis; Figure 2). Yet, they are not restricted to the early states but are an integral part of the disorder and can occur in all states [80–82], that is, within the prodrome of FEP, within prodromal states of relapse, within residual states, and even within acute psychotic episodes; consequently, the assessment of BS can serve several clinical and scientific purposes (Figure 2).

By definition, BS are not evoked by substance misuse or somatic illness and differ from what is considered to be one's "normal" mental self [71]. Being subjective, they remain predominately private and apparent only to the affected person and are rarely directly observable to others but might be indirectly observed by a patient's self-initiated coping strategies in response to BS such as social withdrawal or other avoidance strategies. It is this emphasis on the subjective, self-experienced character that distinguishes BS from (i) negative symptoms in terms of functional deficits observable to others and (ii) frank psychotic symptoms which are experienced by the patient as real and normal thoughts and feelings. The ability to experience BS with insight, however, often attenuates with progressive illness and emerging (attenuated) psychotic symptoms but is commonly restored upon remission [71].

*(2) Assessment Instruments of Basic Symptoms.* Two instruments for the binary assessment of presence or absence of BS were initially developed in concerted action [83]: a semistructured clinical interview, the Bonn Scale for the Assessment of Basic Symptoms (BSABS) [84, 85], and a self-report questionnaire, the Frankfurt Complaint Questionnaire (FCQ) [86]. Nevertheless, the correspondence between BSABS and FCQ subscales was poor, indicating that the mode of assessment is a crucial factor in the evaluation of BS [67, 87].



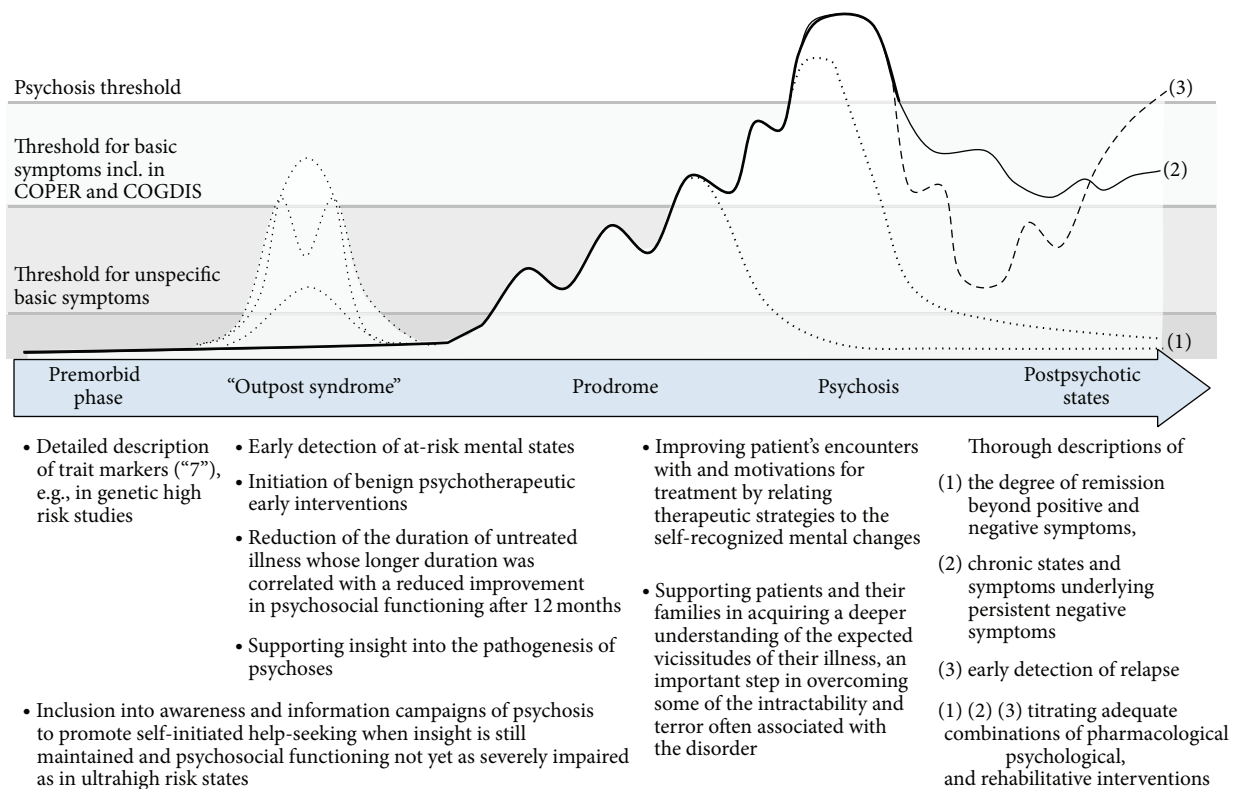


FIGURE 2: Range of possible applications of basic symptom assessment (according to [71, 91]). Annotation: ("7"): SPI-A/SPI-CY rating for basic symptom-like phenomena that are reported as having always been present in the current frequency in a trait-like manner.

Based on the BSABS, we developed an instrument for the quantitative clinical assessment of BS [67, 88], that is, the Schizophrenia Proneness Instrument, in two versions, that is, an Adult (SPI-A; [89]) and a Child and Youth version (SPI-CY; [90, 91]). With regard to the development of the SPI-A, the six BS dimensions in adult samples exhibited a robust structure across samples in different stages of the illness [88]. This structure even remained largely unchanged when BS assessment turned from the binary assessment of presence in the BSABS to an ordinal assessment of frequency-guided severity in the SPI-A. Yet, the structure could not be replicated in a sample of patients with nonpsychotic depressive disorders. Thus, it was concluded that these dimensions might be inherent and unique to schizophrenia and other psychoses and, therefore, can serve as valid and reliable subscales of an instrument for the assessment of BS [88]. Building on this, the final version of the SPI-A was developed after validation on a second prospectively assessed truly prodromal sample [67, 89]. The SPI-A has shown good interrater reliability with an increase of the overall concordance rate with an expert rating from 60% to 89% across five training sessions [67, 89].

Though very consistent in adult samples, the six-dimensional structure of BS was absent in an EOP sample [62, 67]. Rather, a four-dimensional structure was revealed that formed the basis for the subscales of the SPI-CY—thus far the only early detection instrument especially designed for use in children and adolescents aged 8 and older [62, 67, 91].

A striking structural difference between the SPI-A and SPI-CY was that adynamic BS (e.g., lack of energy, motivation, drive, or (positive) feelings including sudden depressive mood, decreased stress tolerance, increased emotional responsiveness, and general cognitive impediments such as concentration, memory, and attention problems or reports of a "blank mind") appeared to play a central role in children and adolescents; this central position was held in adults by mainly cognitive BS, including those included in BS risk criteria described below [67]. The discriminative validity of the SPI-CY was preliminarily confirmed on three groups of children and adolescents: risk patients meeting UHR and/or BS criteria (AtRisk), clinical inpatient controls not suspected to be at risk for developing psychosis (ClinS), and children and adolescents from the general population (GPS) [92]. As expected, the groups differed significantly on all four SPI-CY subscales with the AtRisk sample scoring highest and the GPS lowest and at least moderate between-group effects that were largest for the subscale "Adynamia." However, these results require validation in a larger sample, and longitudinal studies should examine the psychosis-predictive ability of the subscales in different young age groups, especially the role of Adynamia. In cooperation with the Cologne and Zurich University Hospitals for Child and Adolescent Psychiatry, we are currently addressing these questions in a prospective study, the Binational Evaluation of At-Risk Symptoms in Children and Adolescents (BEARS-Kid) study,

TABLE 1: At-risk criterion cognitive-perceptive basic symptoms (COPER) [89, 97].

Presence of at least any one of the following ten basic symptoms with at least weekly occurrence (i.e., a SPI-A/SPI-CY score of  $\geq 3$ ) within the last three months *and* first occurrence at least 12 months ago (irrespective of frequency and persistence during this time):

- (i) thought interference (C2)<sup>a</sup>
- (ii) thought perseveration (O1)
- (iii) thought pressure (D3)
- (iv) thought blockages (C3)
- (v) disturbance of receptive speech (C4)
- (vi) decreased ability to discriminate between ideas and perception, fantasy and true memories (O2)
- (vii) unstable ideas of reference (D4)
- (viii) derealisation (O8)
- (ix) visual perception disturbances, excl. blurred vision and hypersensitivity to light (D5, F2, F3, and O4)
- (x) acoustic perception disturbances, excl. hypersensitivity to sounds (F5, O5)

<sup>a</sup>Item numbers refer to the SPI-A.

TABLE 2: High risk criterion cognitive disturbances (COGDIS) [89, 97].

Presence of at least any two of the following nine basic symptoms with at least weekly occurrence (i.e., a SPI-A/SPI-CY score of  $\geq 3$ ) within the last three months:

- (i) inability to divide attention (B1)<sup>a</sup>
- (ii) thought interference (C2)
- (iii) thought pressure (D3)
- (iv) thought blockages (C3)
- (v) disturbance of receptive speech (C4)
- (vi) disturbance of expressive speech (C5)
- (vii) unstable ideas of reference (D4)
- (viii) disturbances of abstract thinking (O3)
- (ix) captivation of attention by details of the visual field (O7)

<sup>a</sup>Item numbers refer to the SPI-A.

which is funded by a common grant of the Swiss National Science Foundation and the German Research Foundation and examines four groups of altogether 800 children and adolescents (e.g., patients meeting ARMS criteria, inpatients with no clinical suspicion of an ARMS, patients with an EOP, and children and adolescents of the general population) for three years [http://p3.snf.ch/project-144100].

(3) *The Basic Symptom Criteria for an At-Risk Mental State.* The Cologne Early Recognition (CER) study [67, 85, 93–95] was the first ever long-term naturalistic prospective early detection study with a mean follow-up period of 9.6 years and investigated the psychosis-predictive accuracy of BS assessed with the BSABS in 160 adult patients clinically suspected to be at risk for schizophrenia. Based on different types of analyses, two BS criteria that share some of the included BS were developed from its data [67, 85, 93–95]: “cognitive-perceptive basic symptoms” (COPER; Table 1) and “cognitive disturbances” (COGDIS; Table 2).

Compared to COPER, COGDIS seem to have a higher specificity, that is, are associated with higher conversion rates (Table 3), yet this might be at the cost of sensitivity, that is, related to missing more patients who are in fact about to develop a FEP [67]. In other words, COGDIS performed

better in ruling in conversion to psychosis (moderate positive diagnostic likelihood ratio of 3.9), while COPER performed better in ruling it out (moderate negative diagnostic likelihood ratio of 0.23) [93, 96]. Thus, in terms of a clinical staging, these BS criteria were thought to be possibly able to serve different clinical purposes in adult samples, that is, broad risk detection and symptom monitoring based on COPER versus risk detection with the intention to initiate specific psychosis-preventive treatment by COGDIS [93].

Subsequent studies by our group [97–100] and others [101, 102] confirmed the psychosis-predictive ability of both COPER and COGDIS, although conversion rates were somewhat lower at comparable follow-ups (Table 3). This decline might be caused by conservatively accounting for drop-outs as nonconverters [97–100], exclusion of symptomatic UHR criteria [98], age-related peculiarities [102], or other factors related to changes in referral and treatment practice that had been discussed in relation to the much more severe decline in conversion rates observed in UHR samples [103]. In addition, differences in conversion rates might also be related to differences in the BS composition of samples. Analyses of converters of the CER study with different duration of the prodrome defined as short (<1 year), medium (1–6 years), and long (>6 years) revealed group differences particularly in

TABLE 3: Conversion rates for COPER and COGDIS in (sub)samples not systematically treated for psychosis-risk.

| Study             | BS criterion, <i>N</i> ( <i>N</i> criterion positive), predominant age group, <i>n</i> (%) lost-to-last-follow-up of total sample | Conversion rate at month |     |     |     |                  |
|-------------------|---|--------------------------|-----|-----|-----|------------------|
|                   |   | 12                       | 18  | 24  | 36  | >36              |
| [93, 95]          | COPER, 160 (106), adults, n.a.  | 20%                      |     | 37% | 50% | 65% <sup>c</sup> |
|                   | COGDIS, 160 (67), adults, n.a.  | 24%                      |     | 46% | 61% | 79% <sup>c</sup> |
| [97]              | COPER, 146 (146), adults, 60 (41%) <sup>b</sup>   | 25%                      |     | 33% |     |                  |
|                   | COGDIS, 146 (124), adults, 60 (41%) <sup>b</sup>  | 25%                      |     | 33% |     |                  |
| [98] <sup>a</sup> | COPER, 128 (64), adults, 23 (36%) <sup>b</sup>  | 17%                      |     | 20% |     |                  |
| [99, 114]         | COGDIS, 245 (171), adults, 62 (25%) <sup>b</sup>  | 14%                      | 19% |     |     |                  |
| [101]             | COGDIS, 73 (48), adults, n.a.   |                          |     | 25% |     |                  |
| [102]             | COGDIS, 72 (39), adolescents, 15 (21%) <sup>b</sup>   |                          |     | 18% |     |                  |
| [100]             | COGDIS, 246 (158), adults, 56 (23%) <sup>b</sup>  | 23%                      |     | 34% | 40% | 42% <sup>d</sup> |

<sup>a</sup>Supportive counselling control condition only; conversion rate includes conversion to a late state, that is, development of APS or BLIPS.

<sup>b</sup>Those lost-to-follow-up were conservatively regarded as nonconverters, symptomatic UHR criteria excluded.

<sup>c</sup>Minimum of 60 months, maximum of 359 months.

<sup>d</sup>Months 36 to 48.

n.a.: not applicable; only patients with complete follow-up data were included.

cognitive BS constellations that could be interpreted in terms of differences in underlying deficits in information processes, that is, in bottom-up, top-down, or central integrative processes [104]. Because of the current lack of sufficiently long follow-up data, these etiological considerations still await confirmation in independent samples as well as examination in neurocognitive studies.

**3.1.2. Combining Basic Symptom and Ultrahigh Risk Criteria.** Initially developed independently of each other, BS and UHR criteria (Table 4) frequently cooccur and are increasingly applied together—first within our Cologne Early Recognition and Intervention Centre (FETZ), Europe's pioneer early detection service for adults in an ARMS [97, 100, 105, 106]. A combined approach was adopted and first operationalized within the German Research Network on Schizophrenia (GRNS) [107] as a clinical staging model [108, 109] distinguishing an early from a late risk state [110] (Figure 1): an early risk state was alternatively defined by COPER and the UHR state-trait criterion, and a late risk state was alternatively defined by attenuated psychotic symptoms (APS) and brief limited intermittent psychotic symptoms (BLIPS).

The sequence by which symptoms progress according to the clinical staging model for ARMS [107–111]—from unspecific mental problems via first BS of COPER and second APS to psychotic symptoms (Figure 1)—was supported on retrospective data of FEP inpatients [17]. Furthermore, both approaches exhibited good sensitivity in this sample: 79% of the sample reported COPER and 71% APS, whereby 63% reported both APS and COPER [17]. A rather large but not complete overlap between BS and UHR criteria was also apparent in other ARMS studies [97, 99–102, 105].

Moreover, the highest 18-month and 48-month conversion rates showed for the combination of COGDIS and UHR criteria (mainly APS) compared to either COGDIS or UHR criteria alone [67, 99, 100]. For example, within a 48-month follow-up [100], COPER and UHR criteria exclusive of each other revealed hazard rates of 0.23 and 0.28. In line with the GRNS staging model, in the “only UHR” group, conversions occurred between months 1 and 8, while in the

“only COGDIS” group, conversions occurred after month 5 but continued throughout the follow-up thereafter. The combined group “COGDIS plus UHR” showed conversions throughout the 48 months at a hazard rate of 0.66. Notably, irrespective of each other both COGDIS and UHR showed an equal but lower hazard rate of 0.56 [100].

These findings support the merits of considering both COGDIS and UHR criteria in the early detection of persons who are at high clinical risk of developing a FEP; the combination with COPER has not yet been explicitly studied. Applying both sets of criteria improves the sensitivity of risk detection and the individual risk estimation; it may thereby support the development of stage-targeted interventions. Moreover, since the combination of COGDIS and UHR criteria enables the identification of considerably more homogeneous ARMS samples, it should support both preventive and basic research [100]. However, for the still considerable number of false-positive predictions, potential additional predictors enhancing the overall predictive accuracy—ideally without simultaneously reducing sensitivity—continue to be studied at all levels.

**3.2. Searching for Additional Predictors to Enhance Predictive Accuracy.** Across early detection studies, the addition of predictors frequently raised specificity at the cost of sensitivity, that is, frequently leading to a higher rate of exclusion of truly prodromal patients from preventive measures [112]. A possible solution to this dilemma, well-established in somatic medicine, is risk stratification [112, 113]. Risk stratification was first introduced in psychiatric prevention research within the European Prediction of Psychosis Study (EPOS) [99, 114], which used COGDIS and UHR criteria as assessed with the Structured Interview for Psychosis-Risk Syndromes (SIPS; [115]) to detect mainly adult ARMS patients. Examining additional psychopathological predictors, four risk classes for the 18-month conversion risk were identified based on a prognostic index calculated from APS severity, sleep disturbances, schizotypal personality disorder, and functioning and educational level [28]. Notably, the highest risk class contained a much higher percentage (83%) of persons reporting both

TABLE 4: Ultrahigh risk criteria according to the Structured Interview for Psychosis-Risk Syndromes (SIPS) [115].

|  |
|--|
| <p>“Brief limited intermittent psychotic symptom” (BLIPS) syndrome</p> <p>(i) At least any 1 of the following SIPS P-items scored 6 “severe and psychotic”:</p> <p>(a) P1 unusual thought content/delusional ideas<sup>a</sup></p> <p>(b) P2 suspiciousness/persecutory ideas</p> <p>(c) P3 grandiose ideas</p> <p>(d) P4 perceptual abnormalities/hallucinations</p> <p>(e) P5 disorganized communication</p> <p>(ii) First appearance in the past three months</p> <p>(iii) Present for at least several minutes per day at a frequency of at least once per month but less than 7 days</p>  |
| <p>“Attenuated psychotic symptom” (APS) syndrome<sup>b</sup></p> <p>(i) At least any 1 of the following SIPS P-items scored 3 “moderate” to 5 “severe but not psychotic”:</p> <p>(a) P1 unusual thought content/delusional ideas</p> <p>(b) P2 suspiciousness/persecutory ideas</p> <p>(c) P3 grandiose ideas</p> <p>(d) P4 perceptual abnormalities/hallucinations</p> <p>(e) P5 disorganized communication</p> <p>(ii) First appearance within the past year or current rating one or more scale points higher compared to 12 months ago</p> <p>(iii) Symptoms have occurred at an average frequency of at least once per week in the past month</p> |
| <p>“Genetic risk and functional deterioration” (GRFD) syndrome</p> <p>(1) Patient meets criteria for schizotypal personality disorder according to SIPS</p> <p>(2) Patient has 1st degree relative with a psychotic disorder</p> <p>(3) Patient has experienced at least 30% drop in the global assessment of functioning (GAF) score over the last month compared to 12 months ago</p> <p>[1 and 3] or [2 and 3] or all are met</p>   |

<sup>a</sup>Item numbers refer to the SIPS.

<sup>b</sup>In the definition of the Attenuated Psychosis Syndrome of DSM-5, requirements (i) to (iii) are complimented a fourth requirement; that is, significant disability or distress is caused by APS.

COGDIS and UHR criteria than all other risk classes (55–57%).

Other possible psychopathological predictors in adult samples were bipolar, somatoform, and unipolar depressive disorders at baseline, while anxiety disorders at baseline were negatively associated with conversion [116], the Strauss and Carpenter Prognostic Scale items assessing quality of useful work and social relations, positive symptoms and subjective distress [117], presence of ideas of reference and lack of close interpersonal relations as assessed with the Schizotypal Personality Questionnaire [118], and schizoid personality traits but neither schizotypal personality traits [119] nor dimensions of normal personality [120]. Together, these results point to an important role of functional deficits, especially in social contexts, high emotional responsiveness, and severity and persistence of APS in the development of psychosis in adult ARMS patients.

Another line of research on predictors has focussed on deficits in information processing that are common in FEP and have also been observed in ARMS patients, albeit to a lesser degree [121–124]. Objectively assessed neurocognitive deficits were widely independent of the subjectively reported cognitive disturbances included in COPER and COGDIS, thus offering the possibility to explain additional variance between ARMS patients who do or do not convert to psychosis [125]. Conversion was repeatedly related to processing speed deficits and lower premorbid verbal IQ, while results

on the additional value of verbal memory deficits were conflicting [126, 127].

Similar to neurocognitive deficits, also electrophysiological abnormalities have been reported in both psychosis and adult ARMS patients with only slight differences [128, 129]. Abnormalities in mismatch negativity and quantitative EEG parameters have been associated with conversion [130, 131]. Another line of research, which evaluated biochemical abnormalities as potentially valuable predictors, found that anandamidergic upregulation might be a protector against conversion in ARMS patients [132, 133].

As many of these results have been generated independently of one another, future research should use large samples to ensure a sufficient number of converters so that simultaneous analyses of potential predictors and their interactions can be performed. In this way, nonredundant predictors that are most useful for a risk stratification of ARMS patients can be identified. Furthermore, while some of the potential predictors such as functional deficits, greater symptom severity, abnormalities in mismatch negativity, and processing speed deficits have already been replicated by other work groups (see [75] for overview), other results such as the protective role of an anandamidergic upregulation are still in need for replication in independent samples. And last but not least, all potential predictors still need to be studied for developmental differences in children and adolescent samples.



**3.3. Clinical Significance of the At-Risk Mental State.** ARMS patients, however, not only are at risk for future psychosis but also are already suffering from a wide range of mental problems. In addition to the neurocognitive and electrophysiological abnormalities described above, they exhibit poor premorbid adjustment and deficits in psychosocial functioning and subjective quality of life that tend to worsen from the early to the late risk state [134–137]. Notably, a considerable number experience improvement in psychosocial outcome following the detection of an ARMS [138]. Furthermore, many ARMS patients suffer from other nonpsychotic mental disorders, frequently depression and anxiety [105, 116, 139]. Thus it was not surprising that the pattern of coping, self-efficacy, and control beliefs of ARMS patients closely resembled that of depressive patients in its frequent lack of positive coping strategies, low self-efficacy, and a fatalistic externalizing bias [140].

As we and others [75, 141] have shown that help-seeking ARMS samples are clinically significant, in 2008, we raised the question of whether current early detection approaches really target the “prodrome” of psychosis or rather a psychosis-spectrum disorder with a high risk for psychotic symptoms as one of the key questions in early detection research [142]. This issue became widely discussed a year later with the suggestion of including a psychosis-risk syndrome based on APS in DSM-5 [143]. In line with our rationale for a self-contained disorder [112, 144], this proposal was later revised to an APS-based self-contained disorder, the Attenuated Psychosis Syndrome [145]. As such, it was finally included in Section III of DSM-5 as a condition for future studies [146, 147]. Besides questions related to reliability, this decision was made for the unknown prevalence and clinical significance of such a syndrome outside help-seeking samples in the community [147].

**3.4. Risk Criteria and Symptoms in the Community.** The clinical significance of risk symptoms, in particular APS, outside help-seeking samples in the community had been called into question by the high prevalence rates reported for subclinical psychotic symptoms or psychotic-like experiences (PLEs) in the community. PLEs, however, have commonly been assessed by self-report questionnaires or layperson fully structured interviews and thus provide no valid measure of clinician-assessed APS or psychotic symptoms but significantly overestimate their prevalence [148]. Thus it was concluded that dedicated studies are warranted, in which APS—and other risk criteria—are assessed in a way that equates to their clinical evaluation. Supported by a grant from the Swiss National Science Foundation and following confirmation of the reliability of telephone assessments of risk symptoms [149], we started such a study, the Bern Epidemiological At-Risk (BEAR) study, in 2011 (<http://p3.snf.ch/project-135381>). Both an interim analysis of the BEAR study and results from a proof-of-concept study [150, 151] confirmed our expectation that APS criteria and Attenuated Psychosis Syndrome are infrequent: they were met by less than 0.5% of the 1229 mainly adult interviewees that entered the interim analyses of the BEAR study. At symptom level, APS were reported by 13% of the sample and, indicating a clinical significance of APS in the

community, were associated with functional impairments, current mental disorders, and help-seeking although they were not a reason for help-seeking [150]. Future analyses of the full sample of 16–40-year-olds after conclusion of the BEAR study in July 2014 will show if these results are maintained in a larger sample, while comparison with data with the 8–17-year-old community sample of the BEARS-Kid study will help to identify age-related peculiarities that were suggested by Kelleher et al. in their adolescent samples [152]. Furthermore, the aspired follow-up of the BEAR sample will reveal the course and impact of risk symptoms and criteria over time.

As regards BS criteria, COPER and COGDIS and their included BS were as equally rare as APS in the small proof-of-concept study [151], though further confirmation is needed from the larger sample queried in the BEAR study [150]. Furthermore, irrespective of their frequency, any one COPER-BS and any two COGDIS-BS were reported by only 8% and 3% of adolescents in the general population [153].

## 4. Conclusion and Outlook

For the lack of a significant breakthrough in the treatment of psychotic disorders after the onset of the first episode and due to the negative impact of the frequent and often years-long delays in the initiation of an adequate treatment on outcome, hopes are that indicated prevention of psychotic disorders in persons with first signs of the developing disorder will provide such a breakthrough [61, 75, 109, 154, 155]. To this end, an accurate and reliable early detection, that is, the development of exact, broadly applicable, and economic risk criteria, is a prerequisite.

Thus, the accuracy of prediction along with the safety of treatment has been in the main focus of critics and of, sometimes heated, ethical debates [156]. While further research is certainly needed, it is confronted with a dilemma of preventive research: with the growing awareness of the need for treatment in help-seeking ARMS patients and, consequently, its provision, the observation of the long-term natural course of potential risk symptoms that is necessary to develop accurate prediction models is increasingly impossible in clinical samples. The consideration of treatment effects as confounders in prediction analyses however not only raises the need for ever larger samples but also is hindered by the lack of knowledge about their long-term effectiveness [157, 158]. Yet a recent review reported a rather robust overall risk reduction across ten pharmacological and psychological early intervention studies at 12 months of 54% with a number-needed-to-treat of nine [159]. For this reason, *longitudinal epidemiological studies* that reliably and validly assess clinical risk criteria and symptoms in the general population become increasingly important, such as our BEAR study, the first epidemiological study on a large random representative sample of a broad age range and with a sufficient response rate of nearly 70% [150]. Such studies in unselected community samples might also help to alleviate fears about pathologising “normal” experiences that have been raised by reports on frequent and mostly benign PLEs in the community [147]. However, the benign PLEs measured

by self-report in community samples may not be a valid measure of clinician-assessed symptoms [148]. Furthermore, community studies should increase knowledge about help-seeking to detect starting-points for increasing early help-seeking, because, at the currently low rate of only about 30% of FEP patients seeking help prior to the onset of frank psychotic symptoms [13, 14], a significant reduction of the incidence of psychosis—the ultimate target of prevention—will not be in sight. Another question that epidemiological research will help to address is whether to continue to regard current criteria as risk criteria with the main outcome being progression to psychosis and the main treatment target being its prevention or to rather perceive them as a self-contained syndrome in that remission, persistence, and progression, for example, to psychosis, are equally possible outcomes and in that the main treatment targets are current symptoms [112, 144]. In both cases, however, the search for additional predictors of psychosis will continue.

Today, this search mainly relies on group differences that greatly depend on the studied sample and, consequently, are hard to *transfer into clinical practice*, that is, on the risk estimation of an individual patient [127, 140]. Thus, where available such as for neurocognitive or psychological tests, deficits should be defined according to independent test norms, and risk stratification approaches should be presented in a way acceptable to clinicians, that is, not as scores of a complex regression equation but as clear decision rules relying on certain patterns of aberrations [127, 160]. Such a presentation would also facilitate the validation of prediction rules in other samples. The *use of norms* that are generally already gender- and age-adjusted might also help to avoid heterogeneity in data related to gender and, more importantly, *age effects* that have just been started to be addressed in this line of research [62–65, 67, 92, 161, 162], for example, by our multicentre BEARS-Kid study.

Age effects and needs of young age will also have to be considered in *early intervention research* in both ARMS and FEP patients, in particular with regard to more benign psychotherapeutic interventions [161]. Early interventions in an ARMS that have so far mainly focussed on risk symptoms and comorbidities [155, 157] might thereby broaden their focus to enhancing general *resilience factors* such as adequate coping strategies, metacognitive beliefs, or sleep [140, 163].

In summary, while exciting process has already been made in the field of early psychosis—both ARMS and FEP—much remains to be done. And while psychosis research has traditionally been mainly carried out in general psychiatry and adult samples, research on early psychosis and, consequently, rather young patients calls for a stronger involvement of child and adolescent psychiatry and reconsideration of the often strict age-related separation of fields of responsibility of the two professions. A successful example is the FETZ Bern ([http://www.fetz.gef.be.ch/fetz\\_gef/de/index/navi/index.html](http://www.fetz.gef.be.ch/fetz_gef/de/index/navi/index.html)), an early detection and intervention service that serves patients between the ages of 8 and 40—and, at this, the worldwide largest age range—and is run as a cooperation of the Bern University Hospitals for Child and Adolescent Psychiatry, and Psychiatry, and the Soteria Bern.

## Conflict of Interests

Frauke Schultze-Lutter declares that there is no conflict of interests in relation to any subject of this paper. Benno G. Schimmelmann has been a consultant and/or advisor for or has received honoraria from Eli Lilly and Shire.

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